IFW/1711

PATENT
Attorney Docket No. 5273-96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Akira Suzuki et al.	Group Art Unit: 1711
Application No.: 10/526,503	Examiner: Saira Bano Haider
Filed: March 4, 2005	
For: Method for Preparation of Microsphere and Apparatus Therefor	Confirmation No.: 9248

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY

In the Office Action mailed June 12, 2007, the Examiner rejected all of pending claims 1-4, 6, 7, 11-16 and 19-22 under 35 U.S.C. §103(a) for being obvious over a newly cited reference to Suzuki et al. (WO 01/83594), hereafter Suzuki, in view of a newly cited reference to Lenk et al. (U.S. Patent 5,948,441), hereafter Lenk. The withdrawal of all previous grounds of rejection of the claims over Thanoo is appreciated. However, it is believed the pending claims are also patentable over Suzuki and Lenk for the following reasons.

The present invention as defined in amended claim 1 relates to a method for the preparation of microspheres, which comprises the following circulation steps:

(a) emulsifying a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and a

water-immiscible organic solvent having a boiling point lower than that of water into an aqueous solution in an emulsifying device to form an emulsion wherein said medicament-containing polymer solution is dispersed in the aqueous solution;

(b) transferring the obtained emulsion into a microsphere storage tank;

(c) introducing a part of the emulsion from the microsphere storage tank into a cross flow filter;

(d-1)-i)returning a liquid passing over the filter to the microsphere storage tank;

(d-1)-ii) recycling a filtrate filtered from the above cross-flow filter as an aqueous solution for step (a), repeating steps (a) to (d-1), and evaporating said water-immiscible organic solvent in the microsphere storage tank during this circulation process; and

(e) collecting microspheres in the microsphere storage tank after Step (d-1) is completed.

According to this method, the aqueous solution can only effectively be separated from the emulsion prepared in the emulsifying device and transferred into a microsphere storage tank by means of the cross-flow filter and during the circulation process the separated aqueous solution is utilized repeatedly for emulsification and the organic solvent is evaporated off in the microsphere storage tank. This permits the apparatus for preparing the microspheres to be downsized and the production of the microspheres done effectively.

Moreover, according to the present method, even when a large amount of microspheres are produced, the emulsifying scale can be made small, and hence, homogeneous emulsification can be easily done. Consequently, microspheres having a high quality can be obtained. Moreover, because it is carried out in a single apparatus,

the microsphere production scale at any one time can be easily controlled by varying the emulsifying frequency.

Suzuki, which belongs to the same assignee as the present invention, is concerned with a method for the preparation of microspheres from an emulsion, wherein an organic phase containing an organic solvent having a boiling point lower than that of water and a hardly-water-soluble polymer is emulsified in an aqueous phase. The process is characterized by carrying out, with high efficiency, removal of the organic solvent through a gas separation membrane.

It is disclosed in Suzuki, with reference to the U.S. counterpart publication 2003/0094715 beginning in paragraph [0112], that the evaporation of the organic solvent with the gas separation membrane can be done by the following types of methods:

(1) Circulation type

(2) Immersing type

(3) Channel type

As an embodiment of the Circulation type (1), it is disclosed that only a portion of the aqueous phase of the emulsion as a portion of the emulsion is circulated to the gas separation membrane and that the taking of the portion of the aqueous phase of the emulsion is carried out by passing the emulsion through a filter. (See Suzuki et al., paragraphs [0117] and [0118]).

It is also mentioned that the gas separation membrane is in the form of a bundle of plural gas separation membranes which form hollow fibers, in order to enlarge the surface area and that it is preferable to introduce the emulsion into the inner side of the gas separation membrane. Further that . . . by circulating only a portion of the aqueous

phase, it can favorably be passed through into the inner side of the hollow fiber gas separation membrane . . . without clogging of the hollow fiber gas separation membrane. See Suzuki, paragraph [0114] and paragraph [0118]. See also FIG. 1 and Examples 1, 2, 3, 4, 5, and 7, where the emulsion is passed through a stainless mesh filter to separate an aqueous phase and thereafter the aqueous phase is introduced into a silicone rubber hollow fiber membrane module to thereby evaporate off the organic solvent to the outside of the hollow fiber membrane.

As an embodiment of the Immersing type, it is disclosed that the gas separation membrane is a tubular gas separation membrane and in the form of bundles of plural gas membrane which form hollow fibers . . . and that the bundle is immersed in the emulsion and a gas is passed into the inner side of the tubular gas separation membrane. (See Suzuki, paragraph [0129]. See also FIG. 2 and Examples 6, 8, 9, 10, 11, 12, and 13, where the microspheres are prepared by this immersing type of separation method, and the emulsion is located outside of the hollow fiber separation membrane. Hence there is no problem of clogging of the hollow fiber gas separation membrane. No filter is used in this process.

Lenk is concerned with the separation of particles such as liposomes and lipid particles according to particle size using a cross-flow filter. (See Lenk, col.. 1, lines 14-16). It is further mentioned that when liposomes or lipid particles are subject to traditional "dead-end" filtration processes, the problems associated with the filtration of lipids arise as some liposomes or particles may be deformed by the pressures needed to pass them across the filter, but the technique of this invention using a cross-flow filter prevents such problems. (See Lenk , first paragraph).

The Examiner argues that though Suzuki fails to disclose (1) utilization of a cross-flow filter wherein the filtrate is recycled into the emulsifying apparatus, and (2) evaporation of the organic solvent from inside the vessel, that it would have been obvious to do so in view of Lenk.

In reference to the first deficiency of Suzuki, the Examiner points out that Lenk discloses a method for the size separation of particles via tangential flow filtration (or cross-flow filtration) and discloses that cross-flow filtration is better than a traditional filtration process because it prevents filter cake build-up in the filter surface, eliminates dead-end extrusion of larger particles. Therefore, that it would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the cross-flow filter of Lenk in place of the filter in the invention of Suzuki.

In reference to the second deficiency of Suzuki, the Examiner notes that Suzuki discloses the evaporation of the organic solvent inside the vessel, but that it is not in combination with filtration. However, that it would have been obvious to one of ordinary skill in the art at the time of the invention to evaporate the organic solvent from inside the vessel in the process taught by the combination of Suzuki and Lenk.

However, the inventors cannot agree to the Examiner's position for the following reasons.

The present invention is a process for the preparation of microspheres by a circulation process where the emulsion is prepared in an emulsifying device and then transferred into a microsphere storage tank, wherein only the aqueous portion is separated with the cross-flow filter, and the water-immiscible organic solvent is removed from the emulsion within the microsphere storage tank during the circulation process.

The cross-flow filtration is done for the purpose of separating a portion of an aqueous solution from the emulsion and recycling for subsequent emulsification. On the other hand, evaporation of the organic solvent is carried out within the microsphere storage tank separately from the cross-flow filtration which occurs outside of the microsphere storage tank. Both procedures are carried out concurrently and collaterally. This allows the production of microspheres with high efficiency.

On the other hand, in Suzuki, in the circulation type method, the filter is used for the purpose of taking only a portion of the aqueous phase of the emulsion from the microsphere storage tank and passing this portion through to the inside of a hollow fiber gas separation membrane, where the organic solvent is evaporated off. It is then returned to the microsphere storage tank. In the immersing type method, there is no problem of clogging of the hollow fiber gas separation membrane in the step of evaporation of the organic solvent in the microsphere storage tank, and hence, there is no filter.

These are two different types of methods to evaporate off the organic solvent. They are explained separately, and there is not any disclosure or suggestion to combine them or how to combine them. A person skilled in the art would never have thought to carry out such different types of method in combination.

In any event, the filter of Suzuki is used for an entirely different purpose and in a different way from that of the present invention.

As is explained above, in the method of the present invention, the filtrate obtained from the cross-flow filtration is recycled as an aqueous solution back to the emulsification step, i.e., step (a), and the steps (a) to (d-1) are repeated. Moreover, the liquid passing over the filter is returned to the microsphere storage tank. This does not

occur in Suzuki. Rather, in Suzuki the filtrate is passed to the gas separation membrane and it is returned to the storage tank. Thus regardless of whether or not it would have been obvious to substitute the cross-flow filter of Lenk for the filter of Suzuki, the combination still does not teach Applicants' invention as set forth in claim 1. As required by M.P.E.P. §2143, all of the claimed limitations must be taught or reasonably inferred in the prior art to establish a prima facie case of obviousness. The difference in how the processes operate is not insignificant, because in the present process, even when a large amount of microspheres are produced, the emulsifying scale can be made small, and hence, homogeneous emulsification can be easily done. Consequently, microspheres having a high quality can be obtained, and the microsphere production scale at any one time can be easily controlled by varying the emulsifying frequency.

Moreover, the method of Lenk is concerned with the separation of particles according to particle size by utilizing a cross-flow filter, which is clearly different from that of the present invention. That is, the particles to be treated are already-formed particles such as liposome and lipid particles. More specifically, in Examples 1 to 3 in Lenk, the lipid particles (i.e., amphotericin B particles) are separated by a cross-flow filtration, and in Examples 4 and 6, the liposomes containing gentamycin were formed and then were separated by a cross-flow filtration. Further, in Example 5, the lipid particles containing amphotericin B were formed and milled to decrease the average particle size and then separated by cross-flow filtration.

Thus, the method of Lenk is concerned with the separation of already-formed particles according to particle size utilizing a cross-flow filter. This is clearly different from the method of the present invention and of Suzuki of preparing microspheres.

There is no teaching or suggestion in Lenk to separate a portion of an aqueous solution from an emulsion containing an organic phase as a way for forming an emulsion. Consequently, it is submitted that one skilled in the art would not have considered using the cross-flow filter of Lenk in Suzuki in the first place, let alone use it for the purpose claimed.

It is submitted, therefore, that neither claim 1 nor claims 2-4, 6, 7, 11-16, and 19-22 dependent therefrom are obvious over Suzuki in view of Lenk. Their withdrawal as a ground of rejection of the claims under §103(a) is, therefore, requested.

It is believed claims 1-4, 6, 7, 11-16, and 19-22 are in condition for allowance.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: September 12, 2007

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